Introduction to the Cellular and Molecular Biology of Cancer

Second Edition

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3

Epidemiology of cancer

M. C. PIKE and D. FORMAN

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3.1 Introduction

Cancer epidemiology is the study of the pattern of cancer in populations and is essentially statistical, its methods and conclusions being expressed in terms of probabilities, for example 'Japanese women have less than a quarter the breast cancer risk of US women', 'women who have a baby before age 20 have only half the chance of getting breast cancer of women without children', or 'men exposed to benzene have an increased risk of leukaemia'. Its fundamental aim is, of course, to identify preventable (avoidable) causes of cancer, but it also has a critical role to play in many other areas of cancer research, particularly in the evaluation of screening tests to detect cancer at an early stage.

The most basic task of cancer epidemiology is simply to describe the occurrence of human cancer, noting differences, for example, between

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males and females, between persons of different ages, between different socio-economic classes, between persons in different occupations, between different time periods, between different areas of a country, and between different countries. This descriptive epidemiology has been a most fruitful source of ideas as to the possible causes of various cancers. For example, the enormous rise of lung cancer in men, but not in women, between 1920 and 1945 suggested that some recently introduced habit of men, but not of women, must be responsible, and cigarette smoking became the prime candidate. More recently the finding of large differences in the occurrence of colon cancer between different countries has led to intense investigation of the possible role of various aspects of the normal diet (such as fat or fibre content) as factors in the aetiology of this cancer.

3.2 Descriptive epidemiology

3.2.1 *Incidence rates*

To describe the differences in occurrence of a particular cancer between different groups in a meaningful way the most useful concept is that of an incidence rate—the probability of an individual in a particular group being newly diagnosed as having the particular cancer within a year. In epidemiological studies these probabilities are usually expressed not as fractions or decimals but as 'per 100 000', so that, for example, an incidence rate expressed as '200 per 100 000' is identical to an incidence rate of 0.2 per cent or a probability of 0.002. The incidence rate, for example, of breast cancer in females in England and Wales in 1983 was 83.6 per 100 000 (estimated by noting that there were 25 477 800 females in England and Wales on 1 July 1983 and that 21 297 new breast cancer cases were diagnosed in females in England and Wales in that year: 21 297/25 477 800 = 0.000836 or 83.6 per 100 000). We would estimate the equivalent figure for 1981–3 as 83.9 per 100 000 calculated by dividing the 64 079 new breast cancer cases in the three years by the appropriate population of females. Incidence rates are commonly affected by the sex distribution of the people in the reference group, and in this chapter we shall always be referring to single sex reference groups, e.g. the incidence rate of lung cancer in UK females in 1980.

3.2.2 *Age specific incidence rates*

Incidence rates are almost invariably strongly affected by the age of the people in the reference group. For aetiologically meaningful comparisons, incidence rates must be worked out separately for groups of

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persons all of a similar age. The collection of such incidence rates over a span of age groups is referred to as an age specific incidence curve.

Table 3.1 and Fig. 3.1 show the age specific incidence figures for cancer of the colon in females in England and Wales in the period 1979–82. These particular age specific incidence rates display the age incidence pattern seen with most of the important cancers, that is, a rapid increase in incidence with age (a more than 100-fold increase between age 25 and age 70). It has been found most useful to plot both the incidence rate and age on logarithmic scales, because the 'log–log' plot so obtained is, for cancers at many different sites, very close to a straight line (Fig. 3.2). Deviations from the straight line pattern provide important insights into the aetiology of a number of cancers, in particular the major hormone associated cancers of women (breast, endometrium, and ovary).

The age specific incidence curve for breast cancer in females in England and Wales in 1979–82 is shown in Fig. 3.3; there is a roughly linear relationship of the logarithm of incidence with the logarithm of age until about age 50, but then the rate of increase of incidence with increasing age clearly slows down. This incidence curve therefore strongly suggests that something occurs around age 50 in women that acts as a brake on the rate of further breast cancer incidence increases—the obvious candidate is menopause. The protective effect of menopause

Table 3.1 Age specific incidence of cancer of the colon in females in England and Wales (1979–82)[1]

Age	Rate per 100 000
0–4	0.1
5–9	0.0
10–14	0.1
15–19	0.1
20–24	0.3
25–29	0.7
30–34	1.5
35–39	4.2
40–44	7.1
45–49	13.1
50–54	22.5
55–59	36.8
60–64	54.3
65–69	78.8
70–74	109.5

[1] From Muir *et al.* (1987).

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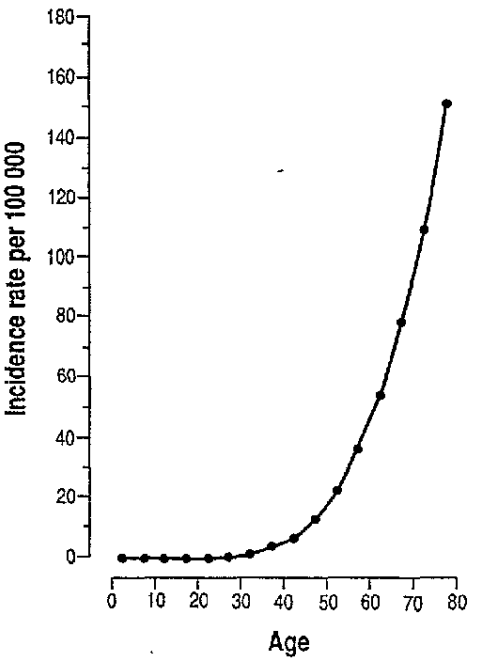

Fig. 3.1 Age specific incidence rates for cancer of the colon in females in England and Wales, 1979–82.

(either natural or resulting from removal of the ovaries) has now been definitely established (see p. 77), and this observation plays a central role in research into the causes and prevention of breast cancer.

The age specific incidence curves of endometrial and ovarian cancer have the same general shape as that of breast cancer. Early menopause also protects against both of these cancers, and provides key insights into the causes of both cancers. We discuss endometrial and breast cancer in more detail below.

The age specific incidence curve for cancer of the testis in males in England and Wales in 1979–82 is shown in Fig. 3.4; there is a peak in incidence around age 30 and then a steady fall. Such a pattern suggests that there is a limited group of susceptible men in the population and that they have almost all been diagnosed with the cancer by middle age. For this and other reasons it is sensible to postulate that the 'susceptible men' are those that have been exposed to some 'carcinogenic agent' either during development in the uterus or in the first few years of life. This hypothesis is now the subject of active research (see p. 83).

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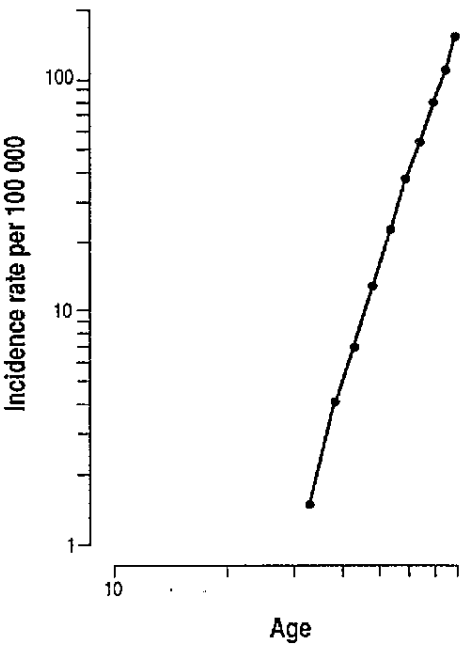

Fig. 3.2 Log–log plot of the age specific incidence rates for cancer of the colon in females in England and Wales, 1979–82.

If the incidence rates for a particular cancer are changing rapidly in time, then the log–log plot of incidence against age for a particular calendar period will not show the true relationship between incidence and age. If incidence rates are increasing, as they did for lung cancer when cigarette smoking became common, then the incidence at old age will be lower than the incidence that the population providing the incidence at young ages will have when they reach old age (see Table 3.5). The log–log plot will thus have too shallow a slope and may even reach a peak before old age and then decline. The opposite phenomenon will be observed if the incidence rates are decreasing. The correct interpretation of an age specific incidence curve, therefore, also requires an understanding of its changes over calendar time.

3.2.3 *Age standardized incidence rates*

Comparisons of age specific incidence curves between different groups for a particular cancer usually show that the pattern of change with age is very similar and it is only the level of incidence that varies. For example,

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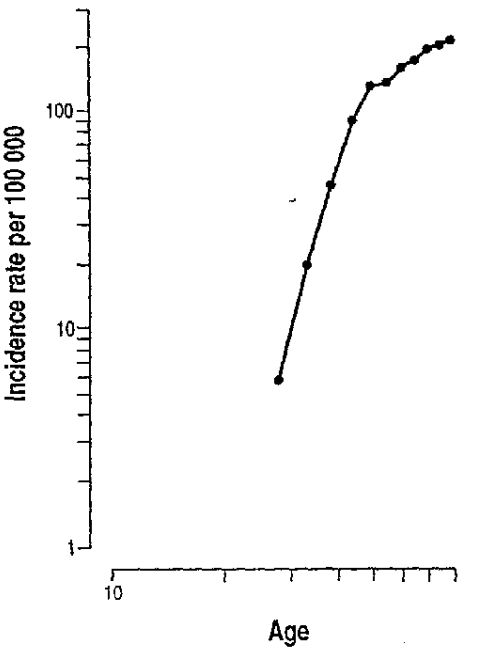

Fig. 3.3 Log–log plot of the age specific incidence rates for cancer of the breast in females in England and Wales, 1979–82.

Fig. 3.5 shows the age specific incidence of stomach cancer in men in Japan in 1973–7 and in the USA in 1969–71. For these situations, comparisons between the different groups can most simply be made by giving a single number representing the level of incidence for each group. The single number chosen is usually taken either as the sum of the incidence rates at each single year of age between, for example, 0 and 74 (the cumulative incidence method) or by using a weighted average of the age specific incidence rates (the age standardized incidence method). The cumulative incidence method gives a number that is the probability that a person gets the specific cancer within the age range considered (if he does not die from any other cause), while the age standardized method gives the incidence in a standard group whose age structure is represented by the weights used in calculating the weighted average; both methods give essentially the same comparative information.

If the pattern of change of incidence with age is not similar in the groups being compared then single numbers cannot, of course, adequately represent the differences between the groups. Cumulative

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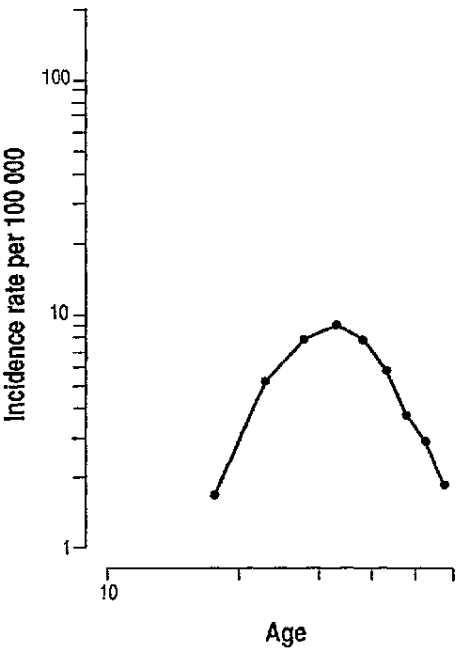

Fig. 3.4 Log–log plot of the age specific incidence rates for cancer of the testis in males in England and Wales, 1979–82.

incidence rates or age standardized rates will still provide valuable information on the occurrence of cancer in the different groups; they need to be supplemented with a description of the age specific patterns in the different groups.

Comparisons of cumulative or age standardized incidence rates between different groups is one of the most commonly used descriptive epidemiological methods. Between-country comparisons of age standardized rates suggest that some 80 to 90 per cent of the current total cancer rate in the UK is caused by environmental and/or behavioural factors and may thus be preventable (discussed later).

3.2.4 *Comparisons between populations*

Table 3.2 shows the cumulative incidence rates (ages 0–74) of breast cancer in different populations around 1970 and around 1980; the rates vary over a more than sixfold range. Japan, China, India, and black Africa have the lowest rates, while the highest rates are observed in

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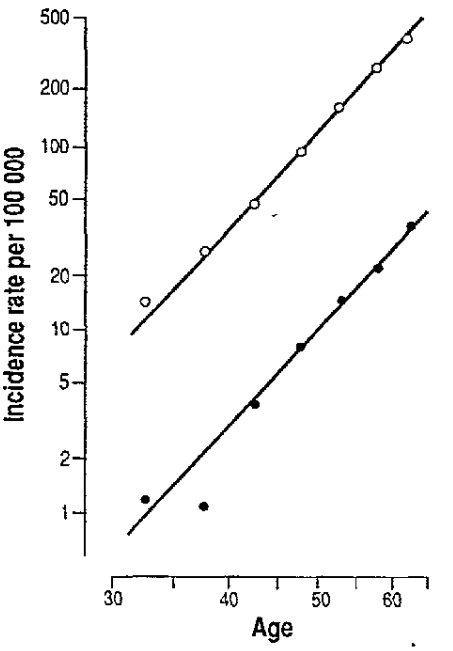

Fig. 3.5 Log–log plot of the age specific incidence rates for cancer of the stomach in males in Miyagi Prefecture, Japan, 1973–7 and in the USA (Third National Cancer Survey), 1969–71.

North American whites. It should also be noted that 16 out of the 19 populations shown in the table, for which rates are available at both points in time, show an increase during the decade considered; in many cases this occurred at a rate in excess of 1 per cent per year. Some part of this increase will undoubtedly be due to more complete cancer registration, but it would also seem that there has been a real increase in incidence.

Table 3.3 shows that Japanese, Chinese, and African immigrants to the USA have breast cancer rates intermediate between those of their country of origin and the USA white population. Blacks in Africa have rates less than one-fifth that of US whites, whereas US blacks have almost three-quarters that rate and at young ages their breast cancer rates are higher than that of US whites. These dramatic effects of migration on breast cancer rates show that environmental and/or behavioural factors are major determinants of breast cancer risk. The fact that a young Japanese American woman now has approximately the

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Table 3.2 Cumulative incidence rates (ages 0–74) of breast cancer in different populations

Population	Cumulative incidence rate (%)	
	c. 1970[1]	*c.* 1980[2]
USA, San Francisco, white	8.9	9.9
Canada, British Columbia	8.8	7.5
Israel, Jews, Europe/USA born	6.5	7.8
USA, San Francisco, black	6.4	7.2
New Zealand, non-Maori	5.8	6.3
Sweden	5.8	6.8
New Zealand, Maori	5.7	6.8
USA, Hawaii, Japanese	5.3	5.5
England and Wales	5.3[3]	6.0
Brazil, Recife	5.1	5.0
Norway	4.9	5.8
USA, San Francisco, Chinese	4.8	4.9
Finland	3.7	4.9
Colombia, Cali	2.9	3.8
Israel, Jews, Africa/Asia born	2.9	5.6
India, Bombay	2.2	2.4
China, Shanghai	2.2[4]	2.1
Singapore, Chinese	2.2	2.9
Nigeria, Ibadan	1.7	N/A
Japan, Osaka	1.3	2.1
Senegal, Dakar	1.3[4]	N/A

[1] From Waterhouse *et al.* (1976).
[2] From Muir *et al.* (1987).
[3] Calculated from England and Wales Cancer Registration Statistics for 1971 (Office of Population Censuses and Surveys 1979).
[4] These rates are *c.* 1975 (Waterhouse *et al.* 1982).

same risk of breast cancer as a British woman means that the low rates of breast cancer in Asia are not simply due to a difference in genetic susceptibility.

Breast cancer is not unusual in showing large differences between incidence rates in different populations; for most cancer sites the pattern of disease in migrants comes to resemble that of their host country in a few generations as they adopt the local lifestyle. A similar effect to that for breast cancer is shown in Table 3.3 for colon cancer in men and in this case Japanese-American rates even exceed the rates in US whites.

Table 3.4 shows the cumulative incidence rates for the common cancer sites in the UK and the percentage reduction in these rates if the lowest observed rate in the world could be achieved in the UK—the reductions are over 70 per cent for most of the major sites, although some of the

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Table 3.3 Cumulative incidence rates (ages 0–74) of female breast and male colon cancer in different populations[1] (*c. 1980*)

	Population	Cumulative incidence rate (%)
Female breast cancer	USA, white	8.84[2]
	USA, Japanese	5.03[3]
	Japan	2.21[4]
	USA, Chinese	4.99[3]
	China	2.03[5]
	USA, black	6.78[6]
	Africa, black	1.47[7]
Male colon cancer	*USA, white*	3.48[2]
	USA, Japanese	3.90[3]
	Japan	1.36[4]
	USA, Chinese	2.95[3]
	China	0.83[5]
	USA, black	3.23[6]
	Africa, black	0.20[7]

[1] From Muir *et al.* (1987).
[2] Weighted means of rates from 8 US Registries (Alameida, Bay Area, Los Angeles, Connecticut, Atlanta, New Orleans, Detroit, Hawaii).
[3] Weighted means of rates from 3 US Registries (Bay Area, Los Angeles, Hawaii).
[4] Weighted means of rates from 4 Japanese Registries (Hiroshima, Miyagi, Nagasaki, Osaka).
[5] Weighted means of rates from 2 Chinese Registries (Shanghai, Tianjin).
[6] Weighted means of rates from 7 US Registries (Alameida, Bay Area, Los Angeles, Connecticut, Atlanta, New Orleans, Detroit).
[7] Weighted means of rates from 2 African Registries [Dakar, Senegal (*c.* 1975) and Ibadan, Nigeria (*c.* 1970); Ibadan figure also includes rectal cancer with colon].

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reductions in Table 3.4 may be inflated due to under-recording of cancers in the low incidence areas. There is clearly tremendous potential for preventing cancer if the environmental and/or behavioural factors responsible for the extreme variations in site specific cancer rates could be identified and people in the UK were prepared to adopt the low-risk behaviour patterns.

3.3 Identifying the causes

In this section we consider, in some detail, the nature of the research findings which underlie our current understanding of the causation of

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Table 3.4 Comparison of England and Wales cumulative incidence rates (ages 0–74) for common cancer sites with the lowest incidence population (*c.* 1980)[1]

Primary site of cancer	Cumulative incidence rate (%)			
	England and Wales rate	Lowest incidence rate[2]	Lowest incidence population	Potential reduction
Males				
Lung	9.15	0.66	India, Madras	93%
Stomach	2.23	0.71	USA, Utah	68%
Prostate	2.17	0.10	China, Tianjin	95%
Bladder	1.99	0.21	India, Nagpur	89%
Colon	1.89	0.26	India, Bombay	86%
Rectum	1.60	0.35	India, Madras	78%
Pancreas	0.94	0.12	India, Madras	87%
Females				
Breast	5.96	1.87	Japan, Miyagi, Rural	69%
Lung	2.42	0.05	India, Nagpur	98%
Colon	1.65	0.27	India, Bombay	84%
Ovary	1.26	0.41	China, Tianjin	68%
Cervix	1.21	0.27	Israel, Non-Jews	78%
Endometrium	1.00	0.12	India, Nagpur	88%
Rectum	0.90	0.16	India, Nagpur	82%
Stomach	0.85	0.31	USA, Utah	64%

[1] Muir *et al.* (1987).
[2] Excluding cancer registry data based on small numbers (less than 1 million person-years).

five specific types of cancer (lung, stomach, endometrium, breast, and testis). We give a brief description of the known and strongly suspected risk factors for the complete range of cancer sites. The five selected sites discussed in this section have been selected for differing reasons and illustrate the principles involved. World-wide lung cancer rates have increased to epidemic proportions and we know precisely why. World-wide stomach cancer rates, in contrast, have been declining and as yet it is unclear why this has happened. Dietary practices are believed to be central to the development of stomach cancer and the difficulties involved in investigating diet and cancer associations are exemplified by research on stomach cancer. Breast, endometrial, and testicular cancer are all presumed to have a strong hormonal dependence. Endometrial cancer is particularly well characterized in this respect and almost every feature of its epidemiology is now understood. Breast and testicular cancer remain more enigmatic and require a more complex consideration of hormonal action.

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3.3.1 *Lung cancer*

Table 3.4 shows that lung cancer is by far the most frequent cancer of UK men and it is also, after breast cancer, the most predominant cancer of UK women. This cancer occupies a unique position among the important cancers in that we have known for at least 35 years the cause of some 90 per cent of it, namely cigarette smoking. This is clearly avoidable. Present epidemiological research interest in lung cancer is mainly focused on identifying subgroups of persons at especially high risk of lung cancer if they smoke and in measuring the risk from passive smoking, i.e. from being exposed to other persons' cigarette smoke. The latter may be particularly important; if passive smoking does cause a significant amount of disease then more stringent control of smoking in public places is clearly called for.

Figure 3.6 shows the trends in male and female lung cancer mortality in England and Wales from 1916 to 1970. Some of the increase in the earlier period is due to improvements in diagnostic accuracy, but the size of the male risk and its continuing increase persuaded scientists and public health officials in the years immediately after the Second World War that the reason for the increase warranted urgent study. That

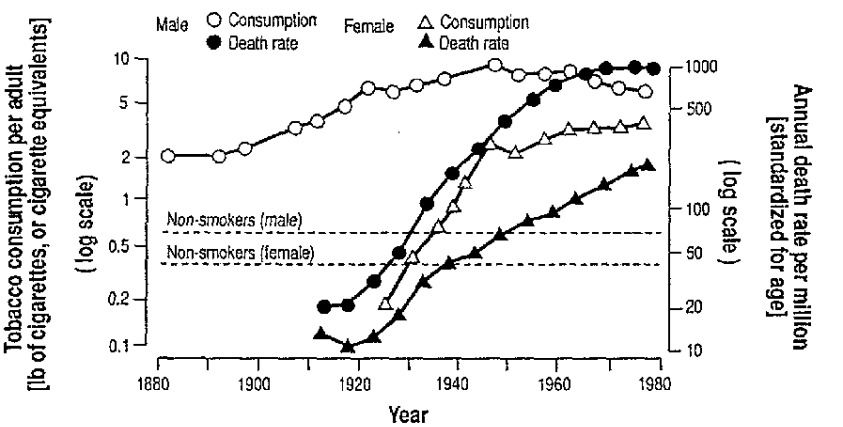

Fig. 3.6 Trends in male and female age standardized lung cancer mortality rates in England and Wales, 1916–70 and cigarette sales per adult. The dotted lines are lung cancer rates found in lifelong non-smokers in cohort studies conducted in the 1950s and 1960s—note that the observed national rates early this century were lower than these rates and these differences in all likelihood are a reasonable measure of the improvements in diagnostic accuracy that have been achieved over the years.

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cigarette smoking could be the cause of the increase was suggested by a number of people and, unbeknown to scientists in the UK and USA, two epidemiological studies conducted in Germany in the late 1930s and early 1940s had, in fact, found a strong association between lung cancer and cigarette smoking. By the end of 1950 a further six case control studies had been published; these studies all compared the cigarette smoking history of lung cancer cases to that of similar men without the disease (controls) and all showed a clear relationship between increasing risk and increasing exposure.

Figure 3.6 also shows how, with women taking up smoking, their lung cancer rates have also increased and how well knowledge of the smoking habits of a population predicts its lung cancer rates some two to three decades later.

There was naturally a great deal of reluctance to accept the findings of the early case control studies—cigarette smoking was an almost universally accepted habit—and many further epidemiological studies were soon initiated, partly to answer criticisms that had been made of the case control studies, but also to investigate whether smoking was associated with cancers of other sites. A number of these epidemiological studies were cohort studies, i.e. studies in which large numbers of people with different smoking habits were identified (in the UK the smoking habits of a large number of doctors were recorded) and their subsequent mortality monitored. These cohort studies not only confirmed the lung cancer/cigarette smoking association but soon established that smoking was also causally associated with cancers at a number of other sites, e.g. tongue, mouth, pharynx, larynx, and bladder (Table 3.10).

Further studies of the relationship of cigarette smoking to lung cancer also showed that stopping smoking has an almost immediate effect on lung cancer risk. The absolute difference between the ex-smoker's lung cancer rate and the lung cancer rate of a non-smoker stays effectively constant with length of time after stopping, rather than continuing to increase as it does for the continuing smoker. These studies showed moreover that the age specific incidence rates of lung cancer of persons in late middle or old age depends on their lifelong cigarette smoking habits, so that age standardized lung cancer rates depend not only on current cigarette consumption in the population but on the cigarette consumption of young adults 40 or more years before. Furthermore, changes in population cigarette consumption may take decades to show up in reduced lung cancer rates in older people.

The tobacco industry responded to the ever mounting evidence of the carcinogenic effects of cigarette smoke by reducing the tar and nicotine content of cigarettes, first by introducing filters and later by modifying the tobacco. The tar content of the cigarettes is probably the relevant

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constituent as regards lung cancer, and the average tar yield per cigarette has steadily declined from approximately 32 mg/cigarette in 1960, to the current level of less than 14 mg/cigarette.

The average number of cigarettes smoked by men in Britain was approximately 10.5/day from 1950 to 1970, but has declined steadily since then and is now approximately 6.5/day. The average number of cigarettes smoked by women in Britain was less than 4/day up until 1960, rose to a maximum of 7/day in the mid 1970s, and then declined; it is now approximately 5/day.

The combined effect of the changed constituents of cigarettes and the average number of cigarettes smoked is shown in Table 3.5. There has been a very significant reduction in male lung cancer incidence; rates are now declining at all ages, except for those currently in their eighties. We can now look forward in this country to an overall two-thirds reduction in the male lung cancer rate even if no further reduction in tar content or cigarette smoking takes place. Female lung cancer rates are also showing a sharp decline at young ages, and although lung cancer rates of older women (over the age of 60 years) are still rising (due to the early adoption of smoking by the present cohort of older women), we can also confidently look forward to a substantial reduction in female lung cancer in the not too distant future.

Unfortunately in many other countries smoking rates are now increasing, especially in young people, in a manner similar to that which took

Table 3.5 Changes in lung cancer mortality rates in England and Wales, 1946 to 1985. (The highest rate for each age group is italicized and bold.)

Age	Death rate per 100 000					Reduction from peak rate to 1981–5
	1946–50	1956–60	1966–70	1976–80	1981–5	
Males						
30–34	***3.6***	3.5	2.5	1.6	1.2	67%
40–44	23.6	***25.1***	21.6	13.8	12.0	52%
50–54	95.4	***124.8***	116.0	99.6	77.0	38%
60–64	171.7	331.5	***369.5***	332.0	300.2	19%
70–74	140.0	387.8	621.0	***662.5***	629.8	5%
80–84	76.5	225.8	456.3	762.3	***833.6***	—
Females						
30–34	1.2	***1.4***	1.1	0.8	0.8	43%
40–44	4.8	6.0	***8.1***	6.2	6.0	26%
50–54	11.7	16.9	28.4	***35.9***	30.0	16%
60–64	22.1	32.8	51.5	84.6	***96.2***	—
70–74	31.6	44.5	73.1	110.5	***141.9***	—
80–84	28.0	45.1	65.7	106.2	***135.1***	—

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place in the UK between 1900 and 1950. As these populations age there will be a large increase in their lung cancer rate. It has been estimated that world-wide as many as 3 million smoking-related lung cancer deaths will occur each year by 2025 compared with about 1 million now. For Europe the 2025 figure has been estimated at 670 000 (480 000 men, 190 000 women) up from the current figure of 260 000 (230 000 men, 30 000 women); the relatively larger increase for women reflects the changes in the number of young women currently taking up smoking. This is clearly a major public health challenge.

Two aspects of the relationship between cigarette smoking and cancer—identifying the genetic constitution of the smoker who is most at risk of lung cancer, and the carcinogenic effects of exposure to other people's cigarette smoke (so called 'passive' smoking)—are presently the focus of much interest. There are clearly large differences between the age at onset of lung cancer in different persons with the same smoking habits. These differences do not prove that different people have different susceptibilities to cigarette smoke induced lung cancer, it may all be simply a matter of chance; they do, however, strongly suggest that there may be different genetic susceptibilities involved. The host factor that has excited most interest is the gene complex coding for the cytochrome P450 enzymes. This controls the metabolic oxidative activation of various chemical carcinogens to an active cancer inducing form (see Chapter 6). The different levels of such enzymes, which are known to be genetically controlled in many animal species, could give rise to wide between-person variation in the generation of carcinogenic derivatives of the chemicals in cigarette smoke. Human studies have focused on two enzyme systems—aryl hydrocarbon hydroxylase (AHH) and debrisoquine 4-hydroxylase.

A number of polycyclic aromatic hydrocarbons (PAHs) that occur in cigarette smoke are potent carcinogens, and the activity of AHH has been closely linked to susceptibility to some PAH induced cancers in animals. The first few studies which compared the AHH activities of lung cancer cases with controls showed a clear difference between the cases and the controls, but subsequent studies have been most confusing and in many cases contradictory. The reasons for the confusion are probably methodological, such as the use of different assay and of different cell types to measure AHH activity. The use of cryopreserved tissue may enable one to circumvent some of these problems, but at present it cannot be stated whether or not AHH activity has any role in human lung cancer. Progress will probably require a different laboratory approach, such as identifying the genes controlling the system.

There has been much recent interest in the enzyme system that metabolizes the anti-hypertensive drug debrisoquine. It is known that

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5–10 per cent of the population have a genetic constitution which makes them incapable of adequately metabolizing the drug and it is thought that such individuals may also be less able to metabolize cigarette smoke constituents into active carcinogens. Two studies have compared debrisoquine metabolism in lung cancer patients and controls, after carefully matching for smoking, and found significant differences between the groups. The authors concluded that either the gene system controlling this oxidation process is also directly involved in cigarette smoke carcinogenesis or that it is closely linked to a gene system which is. Unfortunately the methodology for carrying out debrisoquine metabolism studies is complex and time consuming. It had been hoped that the gene system could be studied directly using DNA screening tests, but this has not so far proved possible.

There is good evidence that parental, particularly maternal, smoking increases respiratory disease rates in young children, and evidence is slowly accumulating that pulmonary function of non-smokers is adversely affected by exposure to smoking by their spouses. Since cigarette smoke is clearly carcinogenic, it is reasonable to assume that involuntary (passive) smoking will also cause a certain amount of lung cancer; the epidemiological question of interest is not really whether or not involuntary smoking causes lung cancer, but how much lung cancer does it cause.

Epidemiological studies suggest that a never-smoker's risk of lung cancer may be increased by some 50 per cent from exposure to other persons' smoke. This estimate has been disputed by a number of researchers who suggest rather that the increased risk of lung cancer seen among never-smokers exposed to passive smoking is largely the effect of certain self-proclaimed never-smokers having at some time been actual smokers. A figure of a 10 per cent increase in risk is suggested by studies of cotinine (a measure of absorbed nicotine) in active and passive smokers. The relationship between the amount of nicotine absorbed and the amount of tar deposited in the lungs is not necessarily the same in passive and active smoking, however, and this could influence the postulated risk in either direction. At present we conclude that it is most reasonable to regard the 50 per cent figure as an upper limit of risk. Further carefully done epidemiological/biochemical studies should resolve some of these issues.

Although cigarette smoking is by far the major cause of lung cancer, exposure to a number of other substances has created a significant added risk of lung cancer for workers in certain industrial occupations. The most important of these has been exposures to asbestos. A substantial number of men previously exposed to high levels of asbestos, particularly in the shipbuilding and insulation industries, have very high lung

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cancer rates. This risk is now universally recognized and the asbestos levels permitted in industry have been very substantially reduced. Occupational exposure to PAHs from the combustion of fossil fuels has also been an important source of added lung cancer risk. High level PAH exposure has occurred particularly to men working in the fumes from coke ovens and in coal gas manufacturing. Other substantial risks to small groups of workers have resulted from exposure to some aspect of the manufacture or refining of chromates, nickel, and copper, and from exposure to radiation from the radioactive gas radon in the air of certain mines (see Chapters 6 and 7).

Radon is not confined to underground areas, but is present in the air in some houses and other buildings where it is not free to diffuse away. Recent advances in techniques for measuring exposure to radon have shown that levels are higher than was previously thought, and current estimates indicate that radon accounts for nearly half the average UK population exposure to ionizing radiation. In the UK the primary determinant of the indoor radon concentration is the underlying geology. In parts of Cornwall and some other areas of the UK the exposure of individuals may be more than 15 times the national average. In some other countries radon exposure from building materials and the radon content of water also influence heavily the indoor radon concentration. Extrapolation from studies of uranium and iron ore miners in North America and Sweden indicate that approximately 5 per cent of all lung cancers may be caused by exposure to indoor radon. If these estimates are correct, radon would be the second most important cause of lung cancer after smoking. Intensive investigation is under way to provide better quantitative information on these risks.

The general population has also been exposed in the past to significant amounts of PAHs in urban air, mainly from the uncontrolled burning of coal. Such general air pollution may have contributed to as much as 10 per cent of all lung cancer in heavily polluted cities but with the passing of various clean air legislation over the years, air pollution has been reduced dramatically and current levels are unlikely to be making more than a small contribution to lung cancer risk.

3.3.2 *Stomach cancer*

World-wide, stomach cancer is the second most important cancer after lung cancer, and it is the most important type in many countries where smoking has become popular relatively recently. The incidence rates for stomach cancer are declining in nearly all countries. This trend has gone furthest in the USA where stomach cancer has been declining since the 1920s and it is now only the sixth most important type. Even countries

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such as Japan and Chile, which have the highest rates in the world, are now showing decreases although the decline started much later than in the USA. The reduction in incidence cannot be attributed to public health policies or to planned interventions. Unlike the situation with lung cancer, no single major causative agent has been identified for stomach cancer and the reasons for its decline are largely unknown. It is of obvious importance to try to understand the reasons for the decline in order to accelerate its rate as, in most of the world, it is still a major contributor to overall cancer mortality.

Many factors have been investigated for a possible association with stomach cancer, but most attention has been paid to diet. This is understandable given that any carcinogens (or anti-carcinogens) in the diet will usually reside in the stomach for several hours before absorption in the small intestine. Diet is extremely difficult to investigate in epidemiological studies mainly because one is interested in obtaining a long-term diet history rather than just a record of what the person has consumed in the immediate past, and even a record of recent food and drink consumption tends to be very unreliable as individuals have great difficulty in recalling (and knowing) precisely what they eat and drink. The usual method of obtaining a diet history is for the cancer patient and matched control groups to indicate on a check list the frequency with which they consume a range of dietary items. At least 12 such dietary case control studies of stomach cancer have been carried out in the last few years.

From these studies four dietary factors stand out and, by and large results have been consistent in all studies. Increased consumption of vegetables and fresh fruit has an appreciable protective effect while consumption of salt and 'preserved foods' tends to increase the risk of stomach cancer. A summary of relevant results is given in Table 3.6. This shows that those in the highest intake group for fruit and vegetable consumption have relative risks of 0.5–0.7, which means they have a 30–50 per cent reduction in risk, compared to those in the lowest intake group. In contrast those with high intakes of salt and 'preserved foods' generally had relative risks in the range 1.5–2.5, indicating a 50–150 per cent increase in risk. The uniformity of these findings in studies from a variety of countries with diverse diets makes it likely that the results represent genuine causal associations.

The results in Table 3.6 beg the question of what mechanisms might be involved. Fruit and vegetables are known to contain a wide range of potentially protective nutrients and it is not possible to state with certainty which ones are critical. Indeed it may be precisely because there are several protective factors that plant products have a noticeable effect. A great deal of research has been carried out on the anti-oxidants contained in fruit and vegetables, particularly ascorbic acid and beta-

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Table 3.6 Relative risks for selected dietary items in recent case control studies of stomach cancer

Country	Year published	Study size		Relative risk at highest intake level[1]				Type of preserved food
		Cases	Controls	Fruit	Vegetables	Salt	'Preserved foods'[2]	
China	1988	564	1131	0.6*	0.4*	1.4	1.4	Salted fish
China	1988	241	241	N/A	N/A	N/A	1.5*	Salted soya paste
Japan	1985	93	86	N/A	N/A	2.6*	2.0*	Pickled vegetables
Italy	1989	1016	1159	0.6*	0.6*	1.5*	2.4*	'Traditional' soup
Italy	1987	206	474	0.7	0.3*	1.5	1.6*	Ham
UK	1989	95	190	0.6	0.3*	6.2*	1.0	Smoked food
UK	1989	149	1934	0.4*	N/A	N/A	N/A	—
Greece	1985	110	110	0.8*	0.7*	N/A	N/A	—
Poland	1986	110	110	0.3*	0.6	N/A	N/A	—
USA, white	1985	194	195	0.5*	0.9	1.4	N/A	—
USA, black	1985	197	195	0.3*	0.5	1.8	2.3*	Home cured meat
Canada	1985	246	246	0.8*	0.8*	N/A	2.6*	Nitrite preserved food

* Relative risk statistically significant for test utilized in study.

[1] Figures show risk of developing stomach cancer for those consuming food at highest level of intake in comparison to those consuming at the lowest level of intake. The categorization of intake levels varies between studies but, most commonly, uses the range of intake in the control population divided into thirds.

[2] Relative risk presented for the item of preserved food showing the most extreme value in the study.

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carotene. As many established carcinogens ultimately exert their effect via an oxidation pathway, potent anti-oxidants should act as anti-cancer agents. More specific evidence in support of such an association comes from studies in which serum levels of beta-carotene were measured in a defined healthy population and comparisons were made between those who subsequently developed stomach cancer and those who remained cancer free. Three such studies have reported results and all three showed a protective effect of high serum beta-carotene levels. In the one study which also measured serum ascorbic acid levels, high levels of ascorbic acid were also found to be protective.

There is much interest in determining whether taking very high doses of the vitamins ascorbic acid and beta-carotene reduces cancer risk and this is being evaluated in controlled trials (see Section 3.4.4). It is unlikely that vitamin supplementation alone will provide the optimal protective effect. Other dietary components are also likely to contribute, e.g. there is evidence from studies in China and Italy that chemicals contained in the allium family of vegetables (onions, garlic, etc.) are protective specifically for stomach cancer and this is not thought to be a vitamin associated effect.

High salt intake increases the risk of stomach cancer, probably by acting as a chronic irritant to the stomach mucosal lining. Over a long time period this would lead to impaired functioning of the mucosa which may result in direct exposure of the stomach epithelial cells to gastric juice. Any toxic or carcinogenic agents in the diet would therefore have a much more intimate contact with target cells. There is also animal evidence to suggest that increased salt intake causes transformed cells to proliferate more rapidly.

Included in the category of 'preserved foods' are a diversity of products and preservation methods. Clearly preservation *per se* is not a single factor and one needs to carefully investigate each of the individual food items. In some cases carcinogens have been identified, e.g. *N*-nitroso compounds in certain preserved meats, pickles, and fish, and in these instances, efforts can be made to reduce or eliminate them. In other cases carcinogens may be present in extremely small quantities and may only pose a problem in communities with a heavy dietary dependence on them. Some preserved foods, e.g. 'traditional' soup in Italy, may not be a problem *per se* but rather a particularly good indicator of an overall poor diet.

Generally a decrease in the dependency on preserved foodstuffs and salt, together with increased availability of fruit and vegetables, offers the best explanation for the world-wide decline in stomach cancer. It is unlikely that these four dietary factors are sufficient to explain the full extent of the decline. In the UK, for example, gastric cancer has declined

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markedly in the past 40–50 years and yet there is very little evidence to suggest that fruit and vegetable consumption has increased, and that salt and pickled food consumption has decreased by a commensurate amount even after allowing for a 20–30 year lag period between dietary change and change in cancer mortality. There have, of course, been other parallel changes in diet and dietary produce, e.g. the introduction of widespread domestic refrigeration and the consequent better food quality, may also play a part.

As well as diet, several other factors have been associated with risk of stomach cancer. Smoking increases the risk about twofold. There is also a strong gradient in risk associated with socio-economic status. Those in manual occupations tend to have a two to threefold increase in risk compared with those in non-manual occupations. Jobs which involve dust exposure, e.g. coal-mining, seem to have a particularly high risk. There are also genetic factors involved, as it has been known for some time that people with blood group A have an excess risk of certain types of stomach cancer.

Stomach cancer is frequently preceded by the development of chronic atrophic gastritis (CAG), i.e. inflammation of the stomach epithelium leading to cellular atrophy, and this has been regarded as a key aetiological event. Metaplastic and dysplastic transformation of epithelial cells occurs much more frequently in people with CAG and such changes frequently precede cancer. A consequence of CAG is loss of gastric acidity because of destruction of acid-secreting cells. All medical conditions that result in CAG and loss of acidity have an excess risk of stomach cancer. Patients with pernicious anaemia, for example, which is usually accompanied by CAG, have been shown to have a three- to fourfold increased risk of cancer.

Attention is now being paid to the causes of CAG. There are several agents that may act as irritants in the stomach and give rise to chronic inflammation. Salt has already been mentioned and coal and other dust particles, and perhaps regular use of certain drugs such as aspirin may act in the same way. Recently there has been a lot of interest in the role of the bacterium *Helicobacter pylori* as a cause of CAG. *Helicobacter pylori* is found exclusively in the stomach where it attaches to the luminal surface of the stomach epithelium beneath the surface mucous layer. There is now considerable evidence to show that *H. pylori* infection can rapidly cause inflammation and acute gastritis, although infection is frequently asymptomatic. Once established in the stomach, *H. pylori* infection seems to be resistant to natural host defence mechanisms, rarely resolves spontaneously, and can be eradicated only with aggressive antibiotic treatment. It is possible that the persistence of the organism will result in a continual inflammatory response and progres-

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sion from acute to chronic gastritis and subsequently to CAG. It is not yet known whether *H. pylori* alone is sufficient for this progression or whether other cofactors are needed. Either way, the *H. pylori* associated gastritis seems to be a precursor of changes that predispose to stomach cancer. *Helicobacter pylori* infection is a relatively common occurrence in many populations and early evidence suggests that, geographically, there is some association between *H. pylori* prevalence and the rate of gastric cancer. Infection at a young age may be particularly important as this would expose the stomach to a chronic inflammatory stimulus for several decades.

Our understanding of what happens to the gastric epithelium after the establishment of CAG owes much to the work of Correa and his colleagues (Correa 1988). He has suggested that the increase in gastric juice pH which accompanies CAG, leads to colonization of the stomach by species of bacteria which can catalyse the formation of intragastric nitrite from nitrate. This nitrite may then nitrosate protein substrates and form carcinogenic *N*-nitroso compounds (NOCs). Such a sequence of events is biologically plausible and all of the individual steps have been demonstrated in studies in man. Also, anti-oxidants such as ascorbic acid are very effective at specifically inhibiting the formation of NOC in the stomach, which may partly explain the protective action of fruit and vegetables. What has yet to be established is whether endogenously synthesized NOCs make any significant contribution to the development of human stomach cancer and, if so, what factors control the rate of formation of these compounds.

Much epidemiological research has been focused on the role of dietary and water-borne nitrate in the synthesis of NOC. The complexity of assessing nitrate exposure has meant that most studies have tended to be correlational in design, i.e. overall population exposures to nitrate have been estimated and compared with relevant stomach cancer rates. This method of inquiry is inevitably crude, but if most of these studies gave consistently positive results it would be hard to avoid the conclusion that nitrate exposure was of significance. The results have been conflicting, a major problem being that in most countries where these studies have been carried out, nitrate intake is mainly derived from vegetable consumption. This means that high nitrate intake tends to be associated with a low cancer risk perhaps because it is also correlated with a high level of ascorbic acid intake. Some studies have looked more specifically at nitrate in drinking water but these too show no consistent pattern of association with stomach cancer. There is only one study that has identified individuals known to have been exposed to high levels of nitrate. They were then followed to see if they developed more stomach cancer than expected. This study involved a group of fertiliser manufacturing

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workers who inhale and ingest nitrate during processing work. Although this was a small study (there were only 12 cases of stomach cancer in the exposed group), there was no indication of any excess of stomach cancer. The lack of positive results does not mean that Correa's model is wrong but that nitrate exposure may not be the rate limiting factor in endogenous NOC formation. It may be that, once CAG is established, there is always sufficient nitrite present in gastric juice to cause nitrosation. In such circumstances what will then be of importance is the presence of nitrosatable protein substrates and modifying agents such as ascorbic acid, which may catalyse or inhibit the nitrosation process. Alternatively NOCs may be just one of several groups of carcinogens present in the stomach from which the epithelial cells are normally adequately protected. The role of CAG would be to diminish both physical and biochemical defence mechanisms by destroying the mucosal layer and cellular integrity.

In summary, there are several leads to understanding the aetiology of stomach cancer but there is no preventive advice that can be given for stomach cancer that would have as dramatic an impact as stopping smoking would have for lung cancer. It is highly likely that increasing fruit and vegetable consumption and decreasing salt intake will reduce risk and one immediate task for epidemiology is to attempt to quantify the level of risk reduction more precisely. It is debatable whether preserved food consumption in the UK makes any material contribution to risk, but in other countries it might. All these dietary modifications would have the additional benefit of reducing circulatory disease. The role of *H. pylori* in stomach cancer requires further investigation. It is apparent that it could be a major cause of CAG but its mode of transmission remains a mystery. Similarly the hypothesis relating nitrates and *N*-nitroso compounds to stomach cancer requires further research before it can be translated into preventive action.

3.3.3 *Endometrial cancer*

Although no carcinogen responsible for endometrial cancer has been identified, the biological basis of the large variation in endometrial cancer rates between different populations and between different groups of women within a population (e.g. between obese and slender women) is now virtually completely understood.

Epidemiological studies have shown that the risk of developing endometrial cancer decreases with an early age at menopause and high parity, increases markedly with increasing weight and with use of oestrogen replacement therapy (ERT) in perimenopausal and postmenopausal women, and decreases markedly with combination type oral

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contraceptive (COC) use (Table 3.7). These risk factors can all be explained in terms of the 'unopposed oestrogen hypothesis' for endometrial cancer.

To appreciate the unopposed oestrogen hypothesis it is essential to understand the production and serum concentrations of the two female hormones, oestrogens (a class of hormones) and progesterone (see also Chapter 13). During the first half of the menstrual cycle—the follicular phase before ovulation takes place—the ovary mainly produces oestrogens, the most important of which is oestradiol (E2). During the second half of the menstrual cycle after ovulation occurs—the luteal phase—the ovary produces both oestrogens and progesterone (Pg). The fluctuating serum concentrations of E2 and Pg during the normal cycle are shown in Fig. 3.7. In the postmenopausal period almost no Pg is produced, but low levels of oestrogens are produced from conversion (mainly in fat cells) of

Table 3.7 Effects of age at menopause, parity, weight, oestrogen replacement therapy, and combination type oral contraceptives on endometrial cancer risk[1]

Risk factor		Relative risk
Menopause (years)	⩽48	1.0
	49–51	1.2
	⩾52	1.7
Parity	0	1.00
	1	0.54
	2	0.22
	3	0.12
	⩾ 4	0.06
Oestrogen replacement therapy (years)	0	1.0
	<1	1.4
	1	2.0
	5–9	6.4
	⩾10	7.6
Current weight (lbs)	⩽129	1.00
	130–149	1.45
	150–169	1.95
	170–189	9.60
	⩾190	17.70
Combination type oral contraceptive use (years)	0	1.00
	<2	0.75
	2–3	0.79
	4–5	0.28
	⩾ 6	0.14

[1] See Key and Pike (1988*a*).

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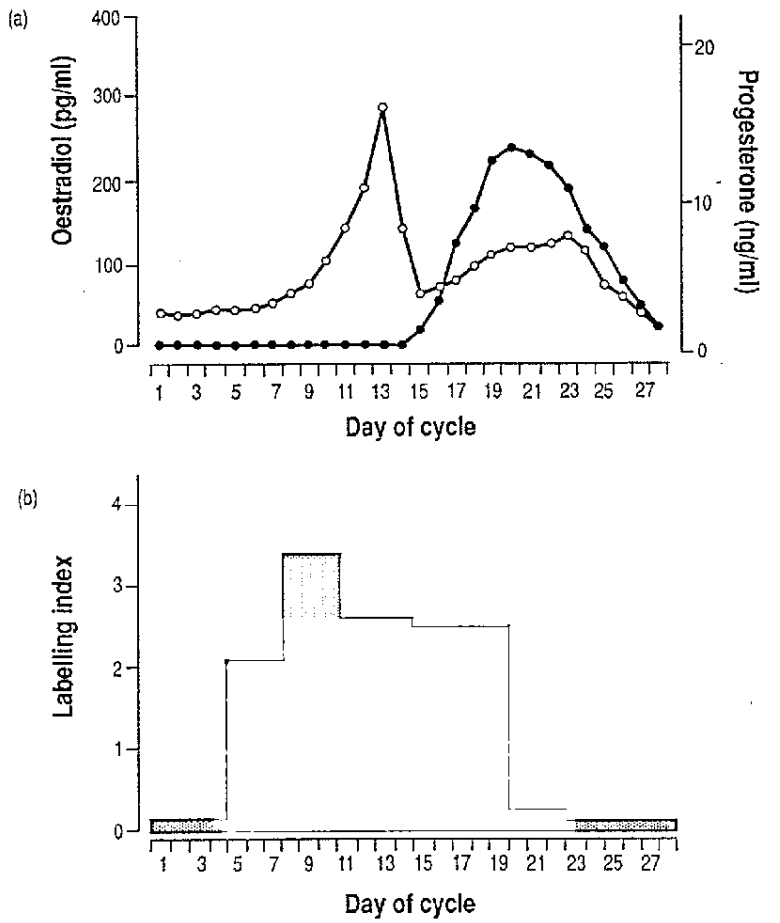

Fig. 3.7 (a) Serum concentrations of E2 (O) and Pg (●) by day of cycle (day 1 is first day of menses and 28-day cycle assumed with ovulation on day 14); and (b) endometrial mitotic rate by day of cycle.

adrenal androgens (male hormones). (These hormones are produced in both sexes.). The concentration of E2 in a slender postmenopausal woman is around 10 per cent (5 pg/ml) of the lowest level found during the normal menstrual cycle.

It is also essential to understand the nature of COCs and ERT. COCs, the commonly prescribed oral contraceptive, contain both a synthetic oestrogen (ethinyl-oestradiol) and one or other of a variety of synthetic

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progestogens (drugs which mimic the action of Pg). ERT, as usually prescribed until recently, simply contains a mixture of oestrogens (all 'natural', but some of equine origin, as the drug is commonly made from the urine of pregnant mares).

The unopposed oestrogen hypothesis maintains that endometrial cancer risk is increased by exposure to oestrogen which is not opposed by progesterone (or a synthetic progestogen), and this increased risk is caused by the increased mitotic activity (cell division) of the endometrium induced by such exposure because oestrogens stimulate mitosis in endometrial cells, only in the absence of progestogens. In women with normal menstrual cycles the mitotic rate rises rapidly from a very low level during menses to reach a near maximal level early on in the cycle, probably by day 5, and then stays roughly constant for 14 days after which it drops to a very low level with the post-ovulation increase in Pg (see Fig. 3.7). The peak mitotic rate is induced by the early relatively low follicular serum E2 concentration (50 pg/ml); later increases in E2 do not increase the mitotic rate further. The very low E2 concentrations of slender postmenopausal women induce very little endometrial cell division.

A smoothed age incidence curve of endometrial cancer is shown in Fig. 3.8. Incidence rises rapidly until about age 50 (average age at menopause) and thereafter at a much reduced rate. The effects of the various risk factors can be most clearly comprehended by noting their effect on this curve. Early menopause reduces risk by reducing the unopposed E2 concentration from the relatively high level during the follicular phase of every menstrual cycle to the very low level of the postmenopausal period; the reduced slope in the postmenopausal period starts at menopause (Fig. 3.9a). Obesity markedly increases the risk of endometrial cancer in premenopausal as well as in postmenopausal women. The mechanism by which obesity increases risk in premenopausal women is Pg deficiency. Obesity is associated with an increased frequency of anovulation (cycles in which no ovulation takes place). There is twice as much endometrial cell division during an anovulatory cycle as during an ovulatory cycle because there will be near maximal endometrial mitotic activity throughout the cycle rather than for only half of the cycle (the serum E2 level will be consistently above 50 pg/ml as even in an anovulatory cycle there is some ovarian follicle development). The further increase in risk with obesity in postmenopausal women is brought about because in such women obesity leads to increased peripheral production of oestrogens from adrenal androgens, and hence to an increased serum concentration of E2. Figure 3.9b illustrates the effect on the age incidence curve. In this figure we show the predicted curve for a woman whose obesity makes her anovular from age 35. Her endometrial mitotic rate for ages 35 to 50 is twice the normal

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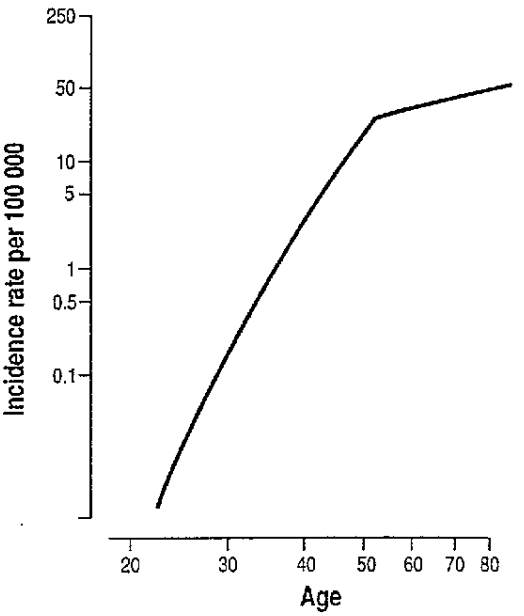

Fig. 3.8 Smoothed age incidence curve of endometrial cancer (from data for West Midlands Region of England, 1968–72).

premenopausal rate. After the menopause her mitotic rate is equal to the normal premenopausal rate (half the follicular rate because bioavailable E2 is approximately half the basal follicular level, but for double the time since there is no luteal phase).

The endometrial mitotic activity of a postmenopausal woman is greatly increased during ERT. The commonly taken dose of conjugated equine oestrogens (CEE, 'Premarin') taken as ERT is calculated to produce an endometrial mitotic rate of between 67 per cent and 100 per cent that occurring during the follicular phase of the menstrual cycle and the total mitotic activity over a 28-day period will be between 1.33 and two-times that of a premenopausal woman. The twofold figure is illustrated in Fig. 3.9c for five years of ERT use starting at menopause (taken as at age 50). Instead of the slope of the incidence curve decreasing at age 50, the slope will actually be steeper for the five years of ERT use. It is predicted that the increased risk will be lifelong, and that five years of such ERT use will increase lifelong risk some 3.5-fold.

Endometrial mitotic activity is near zero in women using COCs. Figure 3.9d illustrates what appears to happen with five years of COC use starting at age 28. The incidence curve will be nearly flat during the

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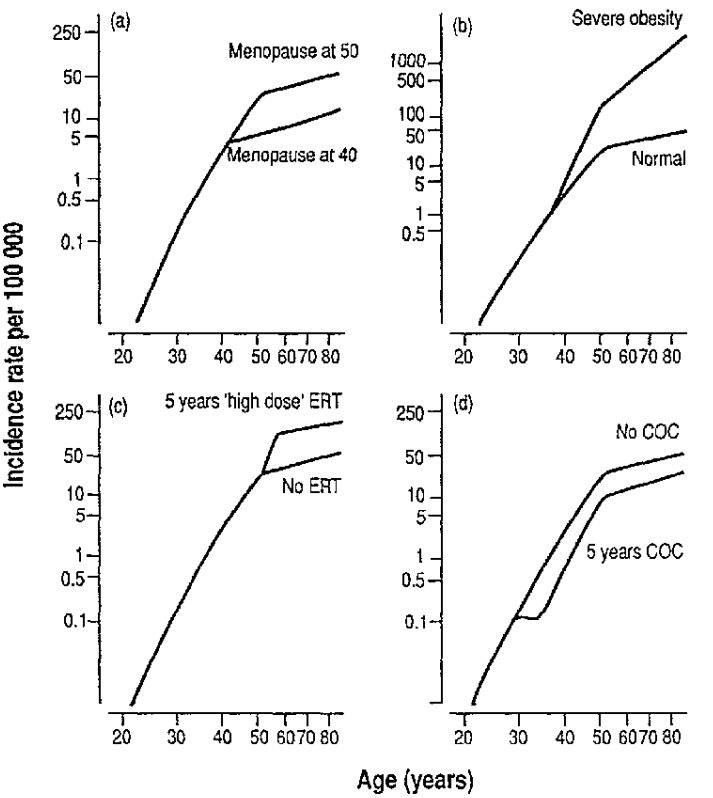

Fig. 3.9 Predicted effects of various 'hormonal' events on the age incidence curve of endometrial cancer (see text): (a) age at menopause of 40 compared to 50; (b) obesity affecting ovulation frequency from age 35 and oestrogen levels in the postmenopausal period; (c) 5 years of 'high-dose' ERT use from age 50 to 55; (d) 5 years of COC use from age 28 to 33.

time COCs are used, and will resume its upward trend when COC use is stopped. The protection against endometrial cancer is predicted to be lifelong, and it is predicted that five years of COC use will decrease lifelong risk by some 55 per cent.

Pregnancies reduce the risk of endometrial cancer because endometrial cells are not exposed to unopposed oestrogen during gestation. As can be seen in Table 3.7 there is a larger reduction in risk between parity 0 and parity 1 than with further increases in parity. This appears to be due to the increased frequency of anovular cycles in certain involuntarily nulliparous women.

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3.3.4 *Breast cancer*

Hormones appear to hold the key to the understanding of human breast cancer, just as they do in certain animal species (see Chapter 13). Recent studies of the causes of the large variation in international breast cancer rates and of the effects on breast cancer of ERT use and of COC use have been particularly useful in advancing our understanding of the nature of the hormonal relationship.

Epidemiological research has established early menarche and late menopause as major risk factors for breast cancer (Table 3.8). A delay of three years in age at menarche has been found to reduce breast cancer risk by up to a half. Similarly the earlier a woman has her menopause the greater the reduction in her breast cancer risk: women with natural menopause before age 45 have only one-half the risk of women whose menopause occurs after age 55. The earlier a woman has her first birth the greater the reduction in her breast cancer risk; women with a first birth under age 20 have about one-half the risk of nulliparous women, but nulliparous women do not have as high a risk as women whose first birth is after age 35. This protective effect of first birth does not appear, however, until some years after the birth; before about age 32 parous women as a group are in fact more at risk of breast cancer than nulliparous women. The overall effect of obesity is to increase the risk of breast cancer, but this increased risk is restricted to older postmenopausal women; in premenopausal women obesity is associated with a

Table 3.8 Effects of age at menarche, age at first birth, and age at menopause on breast cancer risk[1]

Risk factor		Relative risk
Menarche (years)	⩽11	1.00
	12	0.90
	⩾13	0.50
First birth (years)	⩽19	0.83
	20–24	1.00
	25–29	1.30
	30–34	1.57
	⩾35	2.03
	Nulliparous	1.67
Menopause (years)	40–44	1.00
	45–49	1.27
	50–54	1.47
	55–59	2.03

[1] See Key and Pike (1988*b*).

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decreased risk of breast cancer. ERT use in postmenopausal women causes a relatively small increase in risk, while studies of COC use have found either no effect or a relatively small increase in risk.

The success of the unopposed oestrogen hypothesis in explaining and predicting the epidemiology of endometrial cancer has stimulated the effort to develop an equivalent hypothesis for breast cancer.

There is some breast cell division during the pre-ovulatory follicular phase of the menstrual cycle, but the mitotic rate is approximately four-fold higher during the luteal phase. One interpretation of these data is that E2 alone induces some cell division, but that E2 and Pg together (post-ovulatory luteal phase) induce considerably more cell division—the 'oestrogen-plus-progestogen hypothesis'. An alternative interpretation is that breast cell division may only be induced by oestrogens with Pg having little or no effect. This 'oestrogen alone hypothesis' requires there to be a dose response relationship between breast cell division and E2 serum concentration in the range of E2 concentrations occurring during the normal menstrual cycle; there is no such relationship with endometrial cell division, where peak mitotic activity is induced by the low early follicular phase serum oestrogen levels. The breast cell division studies and the lack of a protective effect of COC use, show that an 'unopposed oestrogen hypothesis' for breast cancer is untenable. Current epidemiological evidence is compatible with both the oestrogen alone and the oestrogen plus progestogen hypotheses, although recent evidence tends to favour the latter.

A smoothed age incidence curve of breast cancer is shown in Fig. 3.10. As noted above, there is a steeply sloping line in the premenopausal period and a line with a much shallower slope in the postmenopausal period, with a gradual transition between the two lines during the peri-menopausal period. As with endometrial cancer, the effects of the various risk factors can be most clearly comprehended by noting their effect on the age incidence curve.

Early menarche increases breast cancer risk and, for a given age at menarche, the sooner regular cycles are established the greater the risk of breast cancer. Both E2 and Pg are increased at menarche and by regular cycling, and these observations are compatible with the oestrogen alone and the oestrogen plus progestogen hypotheses. Figure 3.11a illustrates the effect of a three year delay in menarche.

Menopause results in a drastic reduction in both E2 and Pg, and the protective effect of menopause is predicted by both hypotheses. Figure 3.11b compares menopause at age 50 with menopause at age 40. The latter curve has the reduced slope of the postmenopausal period starting at age 40 and the predicted breast cancer risk is decreased by almost 45 per cent.

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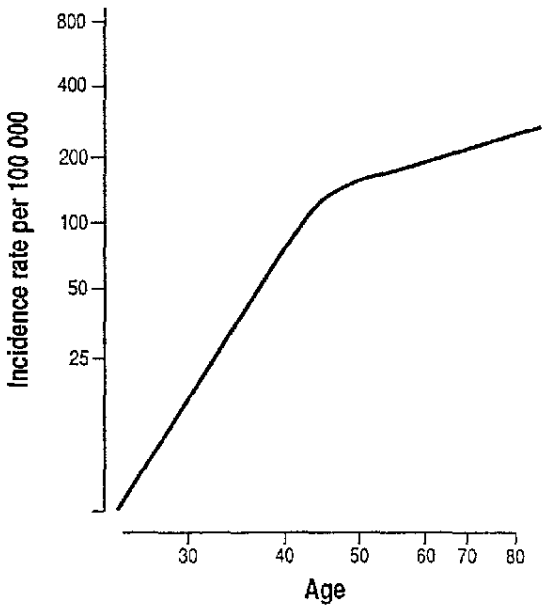

Fig. 3.10 Smoothed age incidence curve of breast cancer (from data for US white women, 1969–71: see Key and Pike 1988*b*).

The contradictory effects of obesity, i.e. an increased risk of breast cancer in postmenopausal women but a reduced risk in premenopausal women, are quite different from the effects of obesity on endometrial cancer, but are, in fact, predicted by both hypotheses. The increased anovulation associated with premenopausal obesity will decrease exposure to both E2 and Pg. This decreased E2 of premenopausal obesity is important as regards breast cell division (on the oestrogen alone hypothesis) since the breast cell division rate induced by the early follicular phase E2 level is much less than that induced (on this hypothesis) by the late follicular and luteal phase oestrogen levels. The decreased risk associated with premenopausal obesity is then gradually eliminated and an increased risk finally achieved by the increased oestrogen levels associated with postmenopausal obesity. Figure 3.11c illustrates the situation. This figure assumes that the breast cell mitotic rate of the obese woman is (i) decreased by 30 per cent in the premenopausal period starting at age 35 and (ii) doubled in the postmenopausal period: the breast cancer risk of such a severely obese woman is reduced by 20 per cent at age 45, is unaltered at age 65, and is increased by 25 per cent at age 80.

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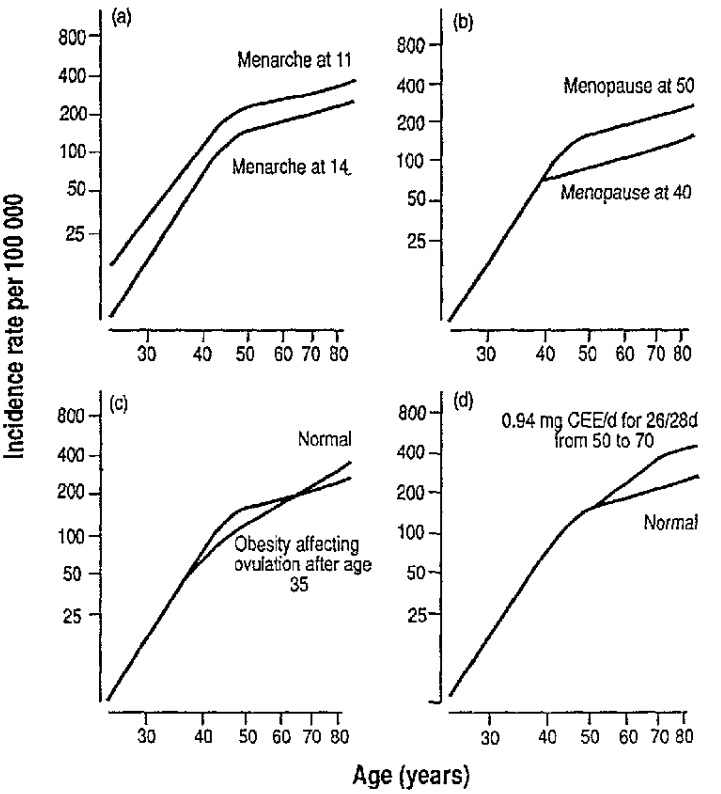

Fig. 3.11 Predicted effects of various 'hormonal' events on the age incidence curve for breast cancer (see text): (a) age at menarche of 11 compared to 14; (b) age at menopause of 40 compared to 50; (c) obesity affecting ovulation frequency from age 35 and oestrogen levels in the postmenopausal period; (d) 20 years of 'high-dose' ERT use from age 50 to 70.

Epidemiological studies of ERT show that an increase in exposure to oestrogen (unopposed by a progestogen) causes a small increase in breast cancer risk. We can estimate from these studies that 20 years of 'old style' standard ERT use causes an approximately 75 per cent increase in risk of breast cancer (Fig. 3.11d). Calculations show that the mitotic rate implied by this 1.75 relative risk is threefold higher than the normal postmenopausal rate and some three-sevenths the average premenopausal rate. This is in line with the known data on oestrogen levels achieved on ERT. The consistency of the oestrogen alone hypothesis with this relatively small relative risk depends on the dose response relationship between oestrogens and breast cell division. ERT produces

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effective oestrogen levels that are sufficient to induce substantial endometrial cell division, but, as we have noted, this does not require high oestrogen levels, and the effective oestrogen level achieved by ERT is certainly less than the effective oestrogen level achieved during the luteal phase of the menstrual cycle. The epidemiological results are thus completely in line with predictions.

COCs have either no effect on breast cancer risk or they slightly increase risk. COCs effectively block ovarian production of oestrogens and Pg, but consist themselves of an oestrogen and a progestogen both at fairly high levels; the epidemiological results (and mitotic rate results from women on COCs) suggest that the breast-effective hormone dose of oestrogen plus progestogen is similar in a normally cycling woman and in a woman on COCs. These epidemiological results are compatible with both the oestrogen alone and the oestrogen plus progestogen hypotheses. Evidence from a recently published Swedish study suggests that the addition of a progestogen to ERT substantially increases the breast cancer risk associated with ERT. If this result is confirmed this will essentially decide between the two hypotheses in favour of the oestrogen plus progestogen hypothesis, and should substantially alter current prescribing habits in which a progestogen is commonly added to ERT.

Detailed study has been made of the extent to which differences in the four major risk factors (ages at menarche, first birth, and menopause, and weight) between Japanese and American women could explain the large differences between their breast cancer rates. Age at first birth has not differed greatly between the two populations, and the distribution of age at menopause appears to vary little between the populations, but Japanese females born around 1900 had an average age at menarche some two years later and they weighed some 22 kg less at age 70 than the 1900 cohort of US white women. Although these differences steadily decreased over the years with the improved nutrition of the Japanese, they accounted for as much as two-thirds of the difference in the observed breast cancer rates in the two countries. They could not, however, account for all the differences—US white women still had 2.5 times the breast cancer risk of Japanese women even after allowing for these factors. To account for this 2.5-fold difference requires a 20 per cent lower breast cell mitotic rate in the premenopausal Japanese women. Such a reduction in premenopausal mitotic rate would result from an approximately 20 per cent reduction in premenopausal hormone levels (averaged over the menstrual cycle). A number of studies in the early 1970s showed lower premenopausal urinary oestrogens in Japanese compared to US women. Recent serum studies, which paid special attention to obtaining samples from Oriental women who were maintaining an old style lifestyle, show clearly lower E2 levels in the

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Oriental women than in US or UK women. These results show that it is reasonable to conclude that the premenopausal E2 levels of the Japanese, who had the four- to six-fold lower breast cancer rates, could easily have been 20 per cent lower than the levels in Western whites. We therefore appear to have a complete hormonal explanation of the difference between Japanese and US breast cancer rates.

International breast cancer incidence and mortality rates are particularly highly correlated with *per capita* consumption of fat (Fig. 3.12). Epidemiological studies of individual breast cancer cases and controls have however provided little support for a role for fat consumption (other than as a major contributor to calories and hence to early menarche and increased postmenopausal weight); and a large prospective study found no relationship between serum cholesterol levels and breast cancer incidence. These studies can, however, be criticized on a number of grounds and further progress in evaluating dietary factors may be more easily achieved by relating premenopausal E2 levels to diet. A number of studies which have compared different racial groups found no evidence that total calories or per cent calories from fat had any effect on premenopausal E2 levels but two studies of US white omnivores and vegetarians, in contrast, show greatly reduced E2 in the vegetarians who consumed a much reduced percentage of calories from fat. Further careful work is clearly needed.

Fig. 3.12 Correlation between international breast cancer mortality rates and per capita consumption of fat.

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On either the oestrogen alone or the oestrogen plus progestogen hypotheses the fact that COC use does not protect against breast cancer suggests, as we noted above, that the total hormone exposure of the breast of a women on COCs is approximately equivalent to her total hormone exposure during a normal menstrual cycle. Both hypotheses suggest that breast cancer risk associated with COC use would be reduced if the total hormone dose of COCs was reduced still further. This does not appear to be possible while maintaining the efficacy of COCs as good contraceptives. However, rather than rely on COC hormones to prevent ovulation one may instead use a luteinizing hormone releasing hormone (LHRH) agonist (LHRHA). LHRHAs will prevent ovulation and the amount of exogenous hormones required to be given to the woman will then be determined solely by the necessity to counteract the harmful effects of the lack of ovarian hormone production; it appears that only a low-dose oestrogen is needed, and calculations strongly suggest that such a contraceptive regimen will significantly reduce breast cancer risk when used by parous women (Pike *et al.* 1989). We are still so ignorant about the relevant events that occur in the breast between menarche and first birth that predicting the benefits or risks of using such drugs at relatively young ages is somewhat speculative. This contraceptive regimen is currently under study.

An alternative approach to the hormonal prevention of breast cancer based on the use of an anti-oestrogen in the postmenopausal period is under active study (Fentiman 1989).

3.3.5 *Cancer of the testis*

Table 3.9 shows that there is a very marked international variation in the incidence of testicular cancer. There has also been a large increase in the incidence rate of the tumour over time in many countries: in England and Wales the incidence rate has increased steadily since the turn of the century and the rate is currently doubling every 25 years. Several studies have attempted to identify specific causes of testis cancer but only urogenital abnormalities, in particular an undescended testis, have been firmly established as having an impact on risk. The distinctive age specific incidence pattern of testicular cancer (Fig. 3.4) must mean that some age related factor is playing a crucial role in causing the tumour. The relevant exposures may occur *in utero* or early in life and/or the germ cells may be susceptible to malignant transformation only at a critical period. What seems clear is that direct exposure to environmental agents cannot, by itself, explain the age-incidence pattern. Factors such as exposure to occupational chemicals can have, at most, only a limited aetiological role.

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Table 3.9 Cumulative incidence rates (ages 0–74) of cancer of the testis in different populations[1] (*c.* 1980)

Population	Cumulative incidence rate (%)
Switzerland, Vaud, Urban	0.73
New Zealand, Maori	0.69
Denmark	0.62
Switzerland, Basel	0.60
Norway	0.45
New Zealand, non-Maori	0.41
USA, San Francisco, white	0.36
Israel, Jews, Europe/USA born	0.30
Sweden	0.26
England and Wales	0.26
Canada	0.23
Colombia, Cali	0.16
Finland	0.12
USA, San Francisco, Chinese	0.10
Japan, Osaka	0.10
Brazil, Fortaleza	0.09
USA, San Francisco, black	0.08
Singapore, Chinese	0.07
India, Bombay	0.07
USA, San Francisco, Japanese	0.05
Israel, non-Jews	0.05
China, Shanghai	0.05

[1] From Muir *et al.* (1987).

The one established major risk factor, namely a prior history of undescended testis (cryptorchidism), has been known for a long time. This condition is associated with an approximately fivefold increase in risk. Cryptorchidism is itself increasing and currently affects some 3.0 per cent of boys in the UK. It is also becoming apparent that cryptorchidism is just one of a range of congenital abnormalities that carry an increased risk of cancer of the testis. It seems that most congenital disorders of the urogenital system are associated with an increased risk of malignancy. These disorders range from gross inherited abnormalities of the genital tract to relatively minor defects, such as infantile inguinal hernia.

Uncorrected and surgically corrected cryptorchid testes appear to be almost invariably associated with the disruption of normal germ cell development. This testicular dysgenesis (loss of germinal epithelium and incomplete maturation of germ cells) starts at a very young age, progresses rapidly, and is often seen in association with carcinoma *in situ*

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(CIS). It is noteworthy that in those situations where dysgenesis is observed in normally descended testes, as in infertile men, there also appears to be a high prevalence of CIS and subsequent malignant cancer. Although dysgenesis only rarely leads to cancer (some 1 per cent of cryptorchid males develop testicular cancer), dysgenesis may be the more immediate cause of the increased cancer risk, and this may occur in several other conditions in addition to cryptorchidism.

Further research on the nature and consequences of urogenital abnormalities is likely to reveal more about the aetiology of testicular cancer not only in men with these problems but possibly also in the large majority who develop the cancer in the absence of any gross urogenital abnormality. Henderson and co-workers have suggested, as a general model, that it is the persistence into adult life of 'primitive' germ cells in a 'developmentally arrested' form that eventually gives rise to a malignant condition (Henderson *et al.* 1988).

Several other factors have been suggested as being involved in cancer of the testis and there has been much interest in the roles of hormonal exposures and genetics. The circumstantial evidence for hormonal involvement is strong. Testicular development and function are both under extremely sensitive hormonal control and animal models have shown that *in utero* exogenous hormone exposures can result in testicular malformations, including cryptorchidism, in offspring. If exposure during the fetal period is important for humans, it could help explain why the incidence of the disease peaks some thirty years later.

A few American studies have shown that maternal use of hormonal preparations, including diethylstilboestrol (DES), during pregnancy will increase the risk of both undescended testis and testicular cancer in male offspring. Relatively few mothers have used such preparations. DES was used in a misguided belief that it could prevent miscarriage, but elevated endogenous maternal hormone levels might have a similar effect. Bioavailable oestrogen levels have been regarded as being particularly important. This is consistent with data from some studies that have associated nausea in pregnancy and high maternal weight with risk of testicular cancer. The first is symptomatic of excess bioavailable oestrogen; increased weight reduces the level of circulating sex-hormone binding globulin, which results in the same effect. The variables concerned are, however, both indirect indications of hormonal exposure, and these relevant findings have come from isolated studies only and have not always been confirmed in other investigations. A recent study found that bioavailable oestradiol levels were higher in first-trimester serum from mothers of cryptorchid boys than from mothers of controls; this offers more direct support for the hypothesis.

Post-natal hormonal exposure may also be relevant at least to the

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extent that testicular cancer does not occur until after puberty when the rise in pituitary hormones stimulating spermatogenesis and testosterone production occurs. One study found early age at puberty to be a risk factor and this could indicate an association between cancer risk and androgen levels. However, if anything, testosterone levels seem to be inversely related to testicular cancer. Despite lower cancer rates, serum testosterone levels are significantly higher in American black men than American white men, and a history of acne, which is associated with high levels of testosterone, has been associated with a decreased risk of testicular cancer. If adolescent hormones are important, the evidence points to pituitary hormones rather than testosterone.

The role of genetics is also an area of active research. As we noted above, there is a large geographic variation in the incidence of cancer of the testis, rates being extremely low in black and Asian populations. This is true also for migrant populations from these populations to countries where the disease is relatively common and therefore appears not to be just a result of different environments. The association between testis cancer and urogenital abnormalities in relatives adds weight to the likelihood of genetic involvement. There is also some evidence of association with particuar HLA (histocompatibility) haplotypes, although there is little consistency between the studies that have investigated this. An increasing number of families with multiple cases of cancer of the testis are now being reported, and it is of relevance to note firstly a higher proportion of bilaterally affected patients in these families and secondly a greater histological concordance between identical twins than between other siblings. Some of these families are now being used to investigate linkage with genetic markers. It is plausible that a genetic lesion may underlie the propensity to testicular dysgenesis and associated urogenital defects.

3.4 Risk factors

Table 3.10 summarizes the known and major suspected risk factors for each cancer site in order of the percentage of all cancer deaths caused by the tumour in the UK in 1986. The incidence and mortality figures give a rough guide to the relative importance of the site as a source of cancer; the relation between the incidence and mortality figures is a measure of the fatality rate associated with the particular cancer; and the male to female ratio for sites common to both sexes suggests the importance of exposure to sex specific risk factors. The established risk factors have been divided into major and minor categories in terms of their importance to the total cancer burden in England and Wales for the specific site. This division is somewhat arbitrary but a major risk factor, perhaps in

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combination with other factors, might account for more than 25 per cent of a particular cancer. Suspected risk factors have only been listed if they are likely to belong in the major category if proven. Table 3.10 also lists, in a separate column, the major established risk factors for cancers in countries other than the UK.

Several aspects of Table 3.10 are noteworthy. Over half of all cancer mortality is accounted for by cancers of the lung, large bowel, breast, and stomach. The other 30 specific sites in Table 3.10 together, therefore, contribute less to total cancer mortality than these four sites. Although, scientifically, there will be much to learn from understanding the aetiological factors for an uncommon cancer, preventing part or even all of the mortality from such a cancer will have only a small impact on total cancer mortality. Minor risk factors for a common cancer may have a much greater public health significance than major risk factors for rarer forms of cancer.

3.4.1 *Smoking and alcohol*

Lung cancer, by itself, accounts for over a quarter of total cancer mortality in the UK. The relationship of smoking with lung cancer has been discussed above. Table 3.10 shows that smoking is also a major established risk factor for cancers of the lip, mouth, tongue, pharynx, larynx, oesophagus, bladder, and pancreas. It is, in addition, a minor risk factor for cancers of the stomach, kidney, and cervix. Smoking is, therefore, a direct and avoidable cause of an enormous cancer burden. No other known single factor has anything like the same degree of importance for cancer in the developed world.

Smoking related cancers in the upper respiratory and digestive tracts, i.e. mouth, tongue, pharynx, larynx, and oesophagus, also share alcohol as an established major risk factor. For the larynx and oesophagus, it has been demonstrated that smoking and alcohol act synergistically, i.e. their effects are more than additive and are, in fact, close to multiplicative. The results of one large study of oesophageal cancer found that a non-drinking smoker of 20 cigarettes per day has a 1.7-fold increased risk, while a non-smoking drinker of 100 g of alcohol per day had a 7.2-fold increased risk, but a 20 cigarettes per day drinker of 100 g of alcohol per day had a 12.1-fold increased risk. Such synergism is not uncommon with cancer risk factors, and shows that control of one risk factor may have a larger effect than one might predict from studies in which people, or experimental animals, were only exposed to the single agent.

3.4.2 *Occupation*

Established carcinogens that occur mainly in occupational settings are

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Table 3.10 Risk factors and certain basic information for the U.K. by specific cancer site[1]

Site (in order of decreasing contribution to mortality)	Incidence (%)	Mortality (%)	M:F	Risk factors			
				Major established	Minor established	Likely major but unproven	Major established but not in the U.K.
Lung	18.1	25.6	2–5:1 at different ages	Smoking	Radon Asbestos Polycyclic aromatic hydrocarbons Arsenic Nickel refining Chromates Bischloromethyl ether	Low intake of beta-carotene rich vegetables[2]	—
Large bowel	12.1	12.3	0.9:1	—	Polyposis coli	Low fibre intake Low vegetable intake High fat intake High meat intake	*Schistosoma japonicum*
Breast	10.7	9.8	0.01:1	Early menarche Late menopause Late first birth	Postmenopausal obesity	High fat intake Hormones (endogenous & exogenous)	—
Stomach	5.5	7.0	1.5:1	Low socio-economic status Achlorhydria Low intake of fresh fruit and vegetables	Blood group A Smoking	*Helicobacter pylori* High salt intake High intake of certain preserved foods	—
Prostate	4.7	4.8	M	Black racial group	—	Hormones (endogenous) High fat intake	—
Pancreas	2.8	4.3	1.0:1	Smoking	Diabetes	—	—
Bladder	4.7	3.3	2.1:1	Smoking	Aromatic amines Certain anti-cancer drugs	—	*Schistosoma haemotobium*
Oesophagus	2.2	3.3	1.4:1	Smoking Alcohol	—	Very hot drinks	Vitamin (A?) deficiency
Ovary	2.3	2.8	F	Early menarche Late menopause	—	—	—

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Oesophagus	2.2	3.3	1.4:1	Smoking Alcohol	—	Very hot drinks	Vitamin (A?) deficiency
Ovary	2.3	2.8	F	Early menarche Late menopause Low parity Oral contraceptives (protective)	—	—	—
Leukaemia	2.1	2.5	1.2:1	—	Ionizing radiation[3] Benzene Certain genetic syndromes Certain anti-cancer drugs	—	Human T-cell leukaemia virus I (HTLV I)
Non-Hodgkin's lymphoma	2.1	2.2	1.1:1	—	Immuno-suppression	—	Epstein Barr virus
Brain and nervous system	1.4	1.7	1.3:1	—	—	—	—
Kidney	1.6	1.6	1.6:1	—	Smoking Aromatic amines Phenacetin	—	—
Cervix	2.0	1.4	F	Multiple sexual partners Low socio-economic status	High parity	Human papillomavirus (specific types only) Smoking Genital hygiene	—
Myelomatosis	1.1	1.4	1.1:1	Black racial group	Ionizing radiation[3]	—	—
Tongue, mouth, and pharynx (excluding nasopharynx)	1.1	0.9	1.6:1	Smoking Alcohol	Oral tobacco	—	Betel quid chewing Inverted smoking

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Table 3.10—*continued*

Site (in order of decreasing contribution to mortality	Incidence (%)	Mortality (%)	M:F	Risk factors			
				Major established	Minor established	Likely major but unproven	Major established but not in England and Wales
Liver	0.5	0.9	1.5:1	Cirrhosis	Hepatitis B virus Anabolic steroids Oral contraceptives Vinyl chloride monomer Thorotrast Immuno-suppression	—	Hepatitis B virus Aflatoxin Liver fluke (*O. viverrini*, *L. siniensis*)
Skin (melanoma)	1.1	0.8	0.8:1	Sun or other ultraviolet light Benign melanocytic naevi White racial group	Xeroderma pigmentosa	Sunburn	—
Endometrium	1.6	0.7	F	Early menarche Late menopause Low parity Exogenous oestrogens (in absence of progestogens) Combined oral contraceptives (protective) Obesity	—	—	—
Gall-bladder and bile ducts	0.6	0.7	0.6:1	Obesity Gall stones	High parity	—	—
Larynx	0.9	0.6	3.8:1	Smoking Alcohol	—	Human papilloviruses (specific types only)	—
Connective tissue	0.4	0.4	1.1:1	—	Immuno-suppression (Kaposis' sarcoma only)	—	—

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Connective tissue	0.4	0.4	1.1:1	—	Immuno-suppression (Kaposis' sarcoma only)	—	—
Hodgkin's disease	0.6	0.3	1.5:1	—	Previous infectious mononucleosis	—	—
Skin (non-melanoma)	11.1	0.3	1.2:1	Sun or other ultraviolet light White racial group	Arsenic Polycyclic aromatic hydrocarbons Xeroderma pigmentosa	—	Tropical ulcers
Pleura and peritoneum	0.3	0.3	5.8:1	Asbestos (some types)	—	—	—
Thyroid	0.4	0.2	0.5:1	—	Ionizing radiation[3]	—	—
Bone	0.2	0.2	1.2:1	—	Paget's disease	—	—
Nose and nasal sinuses	0.2	0.2	1.7:1	—	Nickel refining Hardwood furniture, leather manufacture Isopropyl alcohol production Smoking	—	—
Testis	0.5	0.1	M	White racial group	Undescended testis	Fetal exposure to endogenous hormones	—
Nasopharynx	0.1	0.1	2.4:1	—	—	—	Salted fish Epstein Barr virus HLA type
Salivary gland	0.3	0.1	1.3:1	—	—	—	—
Penis	0.1	0.1	M	Early circumcision (protective)	—	Human papillomavirus (specific types only)	—
Lip	0.2	0.04	9:1	Smoking (esp. pipe) Sun or other ultraviolet light	—	—	—
Choriocarcinoma	0.01	0.003	F	—	—	—	—

[1] Based on Doll and Peto (1987). The incidence figure is for UK cancer registries around 1984: the mortality for UK, 1986: both expressed as proportion of all cancers M:F ratio is for mortality.

[2] Low intake of such vegetables may protect against several types of cancer, although most evidence relates to cancer of the lung (see text).

[3] Ionizing radiation can be a cause of nearly all cancers (excepting possibly chronic lymphatic leukaemia and Hodgkin's disease).

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nearly all categorized as minor risk factors in Table 3.10 (with the exception of asbestos in relation to cancer of the pleura and peritoneum). This does not mean that they are of minor importance for everyone; indeed for workers in the relevant industries they may be of great importance. For example, bladder cancer has been shown to be caused by occupational exposure to a number of chemicals used in the dye and rubber industries. These chemicals (2-naphthylamine, benzidine, 3,3'-dichlorobenzidine, and 4-amino-biphenyl) belong to a class of chemicals, the aromatic amines, which are now known to be animal carcinogens (see Chapter 6). 2-Naphthylamine is particularly carcinogenic; all 19 distillers in one factory developed bladder cancer, and it is no longer used in UK industry. It has been estimated that at most no more than 10 per cent of current bladder tumours are due to occupational exposure. There are several other occupational carcinogens that in the past would have constituted significant health hazards for specific groups of workers. At present, however, only a small proportion of the total cancer mortality experienced by the population as a whole can be attributed to occupational carcinogens.

3.4.3 *Infection*

Although there is an enormous scientific interest in virus-associated cancer (see Chapter 8), infectious agents appear to be of relatively little importance to carcinogenesis in England and Wales. This is very different from the situation in a number of developing countries where, in particular, the risk of liver cancer is enormously raised in persons chronically infected with the hepatitis B virus. For this reason liver cancer is a major cancer in many developing countries. There is also evidence that the Epstein-Barr virus may be aetiologically related to nasopharyngeal cancer and to Burkitt's lymphoma, but this interpretation of the evidence is controversial (see Chapter 8). Bladder cancer risk appears to be associated with chronic infection with the parasite *Schistosoma haematobium*. In England and Wales no infectious agents have been firmly related to cancer (except for a small number of hepatitis B associated liver cancers), but there is a great deal of active research into the role of certain subtypes of the human papilloma virus in cervical and penile cancers (see Chapter 8), and into the role of the bacterium *Helicobacter pylori* in stomach cancer (see p. 69). There is also continuing interest in the role of viral infections in certain types of leukaemia and lymphoma although it is unlikely such associations will be of importance to the forms of these diseases seen most commonly in the UK.

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3.4.4 *Diet*

Dietary factors have been the subject of much epidemiological research in recent years and there is a general belief that modifications to the diet could have a major impact on cancer rates. Table 3.10 indicates that stomach cancer certainly has a major causal dietary component and that lung, large bowel, and breast cancers may have as well. Thus all four major sites could be affected by diet in the UK.

Diet could influence the risk of cancer in many ways. Obesity itself contributes directly to certain cancers, in particular to cancer of the endometrium (see p. 71), so that total calorie intake is important. The direct dietary consumption of known chemical carcinogens also has some role to play. Aflatoxin, a fungal contaminant of peanuts appears to be a major cause of liver cancer in certain tropical countries, while 'natural' chemicals contained in salted fish and bracken fern, which are consumed in parts of Asia, have been linked to cancers of the naso-pharynx and oesophagus respectively. It has not been possible to show that dietary consumption of carcinogens plays a significant role in any human cancer in England and Wales.

Most current research on diet and cancer is concerned with dietary items that would have an indirect link with cancer. A high level of fat intake, for example, has been repeatedly suggested to be a cause of breast (see p. 82) and large bowel cancer. There are strong international correlations between per capita fat consumption and both of these cancers (see, e.g. Fig. 3.12), and studies of Japanese migrants to Hawaii have found an increased fat intake and an increased risk of both cancers. These correlational studies are, however, the crudest form of epidemiological evidence, and studies of fat consumption of cancer patients and controls have provided relatively little support for such relationships. Moreover, prospective studies of serum cholesterol levels which have provided the most compelling evidence of a link between fat consumption and heart disease, have found no evidence whatsoever of a relationship with cancer. It appears, therefore, that if a high fat diet does increase the risk of either breast or large bowel cancer it will have to be some element of such a diet that does not raise serum cholesterol levels.

An exciting area of dietary research is the investigation of the potential protective effect against cancer of beta-carotene, a vitamin A compound. As mentioned in the section on stomach cancer, beta-carotene is one of several micro-nutrients that have anti-oxidant activity (others being ascorbic acid, tocopherol, other carotenoids, and selenium) and all might protect against cancer. Attention has been particularly directed towards beta-carotene because it accumulates in the body in direct proportion to

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intake (no homeostatic balance is maintained) and it has not been associated with any toxic side effects. Beta-carotene can, in addition, be converted to retinol which may have a different mode of protective action as an inducer of cell differentiation.

Nearly all epidemiological studies are consistent with a protective effect resulting from high beta-carotene intake, the most persuasive being those in which beta-carotene levels were measured in serum samples from cases and controls taken several years before the cases developed cancer. Currently, results are eagerly awaited from a number of intervention studies in which participants were randomly divided into two groups that received capsules of either beta-carotene or placebo.

Theoretically beta-carotene intake should reduce cancer risk at many sites. Much attention has been given to its putative role in preventing lung cancer. This is partly because subjects taking part in prospective studies, in which dietary information or serum samples are obtained before cancer develops, will tend to have more lung cancers than any other type. It should be emphasized that even if beta-carotene is genuinely protective against lung cancer, it is unlikely to be able to compensate for the detrimental effects of smoking.

3.4.5 *Other risk factors*

Several factors which are often associated with cancer are either not included in Table 3.10 or are categorized as minor factors. Industrial pollution, pesticide exposure, and psychological stress are not listed at all. A number of these omissions may reflect a failure of cancer epidemiology to investigate certain subjects (e.g. stress) adequately but these omissions also reflect the fact that although many chemicals are reported as positive in animal carcinogenicity or *in vitro* tests (see Chapter 6), they appear to make a negligible contribution to human cancer. In some cases this is because the doses employed in testing are orders of magnitude above those to which people are exposed. It is now also apparent that the human body is continually confronted with genotoxic (DNA damaging) agents not only from industrial chemicals but also from a wide range of products found naturally in many foods (Ames *et al.* 1987). It may, therefore, prove to be the case that many genotoxic agents will be of much less importance to human cancer than, say, host DNA repair mechanisms or factors which stimulate cells to proliferate. Clearly some genotoxins are of considerable importance, for example, u.v. light and the carcinogens present in tobacco smoke. Others may be of limited relevance to human cancer.

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3.4.6 *Summary*

A comprehensive overview of our current understanding of the causes of all types of cancer has been made by Doll and Peto (1981, 1987) and their conclusions are summarized in Table 3.11. Tobacco (more specifically cigarette smoking) stands out in that it accounts for an estimated 30 per cent of all cancer mortality and it is the only factor for which all the associated deaths could undoubtedly be avoided by the implementation of known practical measures.

Dietary modifications could perhaps avoid a greater number of cancer deaths than changes in smoking (maybe 35 per cent), but our ignorance of the specific changes required means that there is a lot of uncertainty in the estimate of what is possible (10–70 per cent) and there are very few changes that could be immediately taken up that would be certain to reduce risk.

The contribution of occupational risk factors to the total population

Table 3.11 Proportions of cancer deaths in the USA[1,2] attributable to various factors

Factor or class of factors	Per cent of all cancer deaths		
	Best estimate that potentially could be avoided	Range of acceptable estimates	Known to be avoidable now
Diet	35	10–70	2
Tobacco	30	25–40	30
Reproductive factors	7	1–13	?[5]
Occupation	4	2–8	<1
Alcohol	3	2–4	3
Geophysical factors	3[3]	2–4	<1
Pollution	2	<1–5	<1
Medicines and medical procedures	1	0.5–3	<1
Food additives	<1	—5[4]–2	<1
Industrial products	<1	<1–2	<1
Infection	(10)	1–?	<1

[1] After Doll and Peto (1981, 1987).

[2] Similar figures would apply to the UK.

[3] 'Only about 1%, not 3% could reasonably be described as "avoidable". Geophysical factors also cause a much greater proportion of non-fatal cancers (up to 30% of all cancers, depending on ethnic mix and latitude) because of the importance of u.v. light in causing the relatively non-fatal basal cell and squamous cell carcinomas of sunlight-exposed skin' (Doll and Peto 1981).

[4] 'Allowing for a possible protective effect of antioxidants and other preservatives' (Doll and Peto 1981).

[5] Manipulation of some reproductive factors (e.g. age at first birth) to avoid cancer is clearly possible but not necessarily practical or acceptable.

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cancer burden is estimated as being no more than 8 per cent, and probably closer to 4 per cent. Occupational exposure to established carcinogens has been substantially reduced, e.g. asbestos, or entirely eliminated, e.g. 2-naphthylamine, in England and Wales, so that there are very few practical measures that could be implemented now which would guarantee a reduction in occupationally related cancer.

Reproductive factors, such as age at first birth and number of children, can account for some 13 per cent of cancer mortality. It is however not likely that women would manipulate such factors to prevent cancer, since these factors are so important to everyday living and having an early first birth, for example, may have other unwanted 'side-effects'. All hormone-related cancers may be controllable in the future by use of appropriate drugs in a manner similar to the way in which oral contraceptives reduce endometrial and ovarian cancer; this idea should not be thought of as interfering with nature any more than, for example, delaying first pregnancy.

Further details of the calculations that underlie Table 3.11 can be found in Doll and Peto (1981) while their more recent publication (1987) expands on our discussion of risk factors on a site by site basis.

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